Supplemental Material

Definition of unstable angina used in the ODYSSEY studies

A diagnosis of an unstable angina (new ACS event without elevation in cardiac biomarkers) that meets the primary endpoint requires the following:

- Admission to hospital or emergency room (until at least next calendar day) with symptoms presumed to be caused by myocardial ischemia with an accelerating tempo in the prior 48 hours. and/or prolonged (at least 20 minutes) rest chest discomfort

AND

- New high-risk ECG findings consistent with ischemia (or presumed new if no prior ECG available), as defined below:
  - New or presumed new ST depression >0.5mm in 2 contiguous leads or T wave inversion >1mm in leads with prominent R wave or R/S >1 in 2 contiguous leads
  - New or presumed new ST elevation at the J point in >2 contiguous leads >0.2mV in V2 or V3 in men or >0.15 mV in women in V2 or V3 or >0.1mV in other leads
  - LBBB (new or presumed new)

AND

- Definite contemporary* evidence of angiographically significant coronary disease as demonstrated by:

– Need for coronary revascularization procedure (PCI or CABG) excluding those performed to treat only restenosis lesion(s) at previous PCI site(s)

OR

– Angiographic evidence of at least 1 significant (> 70%) epicardial coronary stenosis not due to restenosis at previous PCI site.

*The coronary revascularization procedure or the diagnostic angiography must have been performed during the hospitalization for that event.

eTable 1. Key inclusion and exclusion criteria for trials included in this analysis

Study	Inclusion criteria	LDL-C exclusion criteria
FH I, FH II[1]	Patients with HeFH not adequately controlled with a maximally-tolerated stable daily dose of statin* for ≥4 weeks prior to screening ± other LLT	LDL-C <70 mg/dL (for patients with documented clinical ASCVD) or LDL-C <100 mg/dL (for patients with no documented ASCVD)
HIGH FH[2]	As above	LDL-C <160 mg/dL.
COMBO I,[3] **COMBO II**[4]	Patients with hypercholesterolemia (non-FH), not adequately controlled with a maximally-tolerated stable daily dose of statin* for ≥4 weeks prior to screening (± other LLT in COMBO I; no other LLT allowed in COMBO II)	LDL-C <70 mg/dL (for patients with documented clinical ASCVD) or LDL-C <100 mg/dL (for patients with no documented ASCVD)
LONG TERM[5]	Included both HeFH and non-FH patients, otherwise inclusion criteria as for the FH studies above	LDL-C <70 mg/dL.
OPTIONS I,[6] **OPTIONS II**[7]	Patients with HeFH or non-FH, receiving either atorvastatin 20 or 40 mg (OPTIONS I) or rosuvastatin 10 or 20 mg (OPTIONS II) ± other LLT (apart from ezetimibe as it was used as a comparator)	LDL-C <70 mg/dL (for patients with documented clinical ASCVD) or LDL-C <100 mg/dL (for patients with no documented ASCVD)
ALTERNATIVE[8]	Patients with HeFH or non-FH and documented statin intolerance† and moderate to very high cardiovascular risk;‡ patients were not receiving a statin but other LLT (apart from ezetimibe) were allowed	LDL-C <70 mg/dL for very-high risk, LDL-C <100 mg/dL for moderate or high risk
MONO[9]	Subjects with 10-year risk of fatal CV events of ≥1% and 5% based on the European Systematic Coronary Risk Evaluation (SCORE)[10] not receiving statin or other LLT (history of CHD or HeFH was an exclusion criterion for this study)	LDL-C <70 mg/dL or >190 mg/dL
Exclusion criteria common to all studies	• Age <18 years • Use of fibrates, other than fenofibrate	

	• Fasting serum triglycerides >400 mg/dL • Estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2

Clinicaltrials.gov identifiers: LONG TERM, NCT01507831; FH I NCT01623115; FH II, NCT01709500; HIGH FH, NCT01617655; COMBO I, NCT01644175; COMBO II, NCT01644188; MONO, NCT01644474; OPTIONS I, NCT01730040; OPTIONS II, NCT01730053; ALTERNATIVE, NCT01709513.

ASCVD, atherosclerotic cardiovascular disease; LLT, lipid-lowering therapy.

*Maximally tolerated statin dose = the highest tolerable registered dose of daily statin currently administered to the patient, i.e. rosuvastatin 20 or 40 mg, atorvastatin 40 or 80 mg; or simvastatin 80 mg. Lower doses could be used e.g. in the case of intolerance or local practice according to the investigator's judgment.

†Inability to tolerate 2 or more statins because of muscle-related symptoms.

‡Moderate risk = 10-year risk of fatal CV events of ≥1% and 5% (SCORE); high risk = SCORE ≥5%; eGFR 30 to <60 mL/min/1.73 m^2; type 1 or 2 diabetes mellitus without target organ damage; or HeFH; very-high risk = CHD, ischemic stroke, peripheral artery disease, transient ischemic attack, abdominal aortic aneurysm, or carotid artery occlusion >50% without symptoms; carotid endarterectomy or carotid artery stent procedure; renal artery stenosis or renal artery stent procedure; or type 1 or type 2 diabetes mellitus with target organ damage.

References

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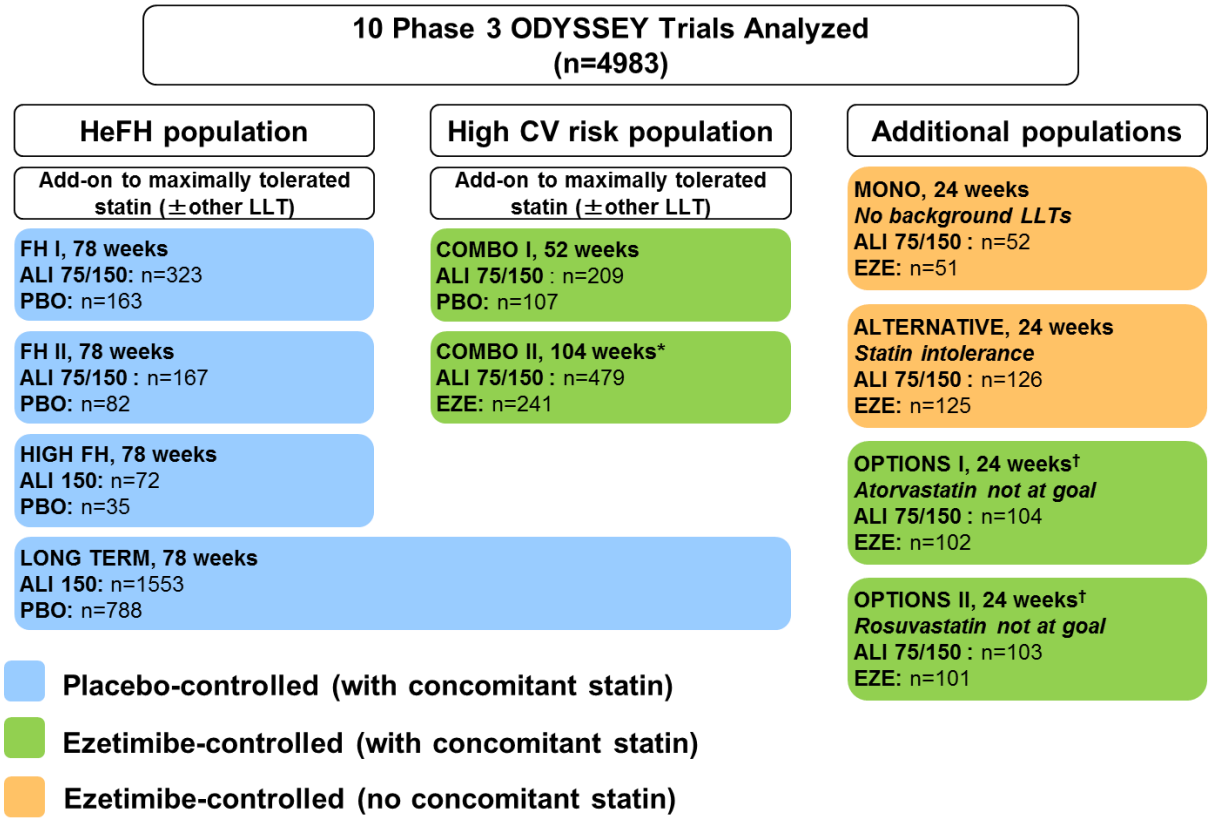
eFigure 1. Overview of studies included in this analysis



ALI, alirocumab; CV, cardiovascular; EZE, ezetimibe; HeFH, heterozygous familial hypercholesterolemia; LLT, lipid-lowering therapy; PBO, placebo; Q2W, every 2 weeks.

ALI 75/150 indicates studies using a dose titration strategy, whereby ALI 75 mg Q2W was increased to 150 mg Q2W at Week 12 if LDL-C at Week 8 was ≥70 mg/dL (or, in OPTIONS I, OPTIONS II, and ALTERNATIVE, ≥70 or 100 mg/dL, depending on CV risk). ALI 150 indicates studies where patients received 150 mg Q2W from the outset. In all but two studies, patients also received background statin therapy ± other LLT (EZE was not allowed as background LLT in EZE-controlled studies). The statin was at maximally tolerated dose in 6 studies (85% of all patients in the 10 trials). Under "additional populations", 2 studies were performed without background statin (ALTERNATIVE, in patients with documented statin intolerance, and MONO, a monotherapy study performed without background LLT). OPTIONS studies included patients at high CV risk receiving moderate to high doses of potent statins.

*No other non-statin LLT allowed in COMBO II. †Concomitant statin and doses were atorvastatin 20 or 40 mg in OPTIONS I and rosuvastatin 10 or 20 mg in OPTIONS II.

eTable 2. Baseline characteristics in Phase 3 ODYSSEY trials (randomized population)

Study	Group	Age, years, mean (SD)	Male, n (%)	Race, white n (%)	BMI, kg/m^2, mean (SD)	HeFH, n (%)	Type 2 diabetes, n (%)	ASCVD, n (%)
Placebo-controlled								
LONG TERM (MTD statin)	ALI 150 (n = 1553)	60.4 (10.4)	983 (63.3)	1,441 (92.8)	30.2 (5.7)	276 (17.8)	545 (35.1)	1,187 (76.4)
	PBO (n = 788)	60.6 (10.4)	474 (60.2)	730 (92.6)	30.5 (5.5)	139 (17.6)	269 (34.1)	612 (77.7)
HIGH FH (MTD statin)	ALI 150 (n = 72)	49.8 (14.2)	35 (48.6)	64 (88.9)	28.8 (5.2)	72 (100)	9 (12.5)	32 (44.4)
	PBO (n = 35)	52.1 (11.2)	22 (62.9)	30 (85.7)	28.9 (4.2)	35 (100)	6 (17.1)	22 (62.9)
COMBO I (MTD statin)	ALI 75/150 (n = 209)	63.0 (9.5)	131 (62.7)	170 (81.3)	32.6 (6.3)	0	94 (45.0)	179 (85.6)
	PBO (n = 107)	63.0 (8.8)	77 (72.0)	88 (82.2)	32.0 (7.1)	0	42 (39.3)	87 (81.3)
FH I (MTD statin)	ALI 75/150 (n = 323)	52.1 (12.9)	180 (55.7)	300 (92.9)	29.0 (4.6)	323 (100)	32 (9.9)	154 (47.7)
	PBO (n = 163)	51.7 (12.3)	94 (57.7)	144 (88.3)	30.0 (5.4)	163 (100)	25 (15.3)	81 (49.7)
FH II (MTD statin)	ALI 75/150 (n = 167)	53.2 (12.9)	86 (51.5)	164 (98.2)	28.6 (4.6)	167 (100)	7 (4.2)	63 (37.7)
	PBO (n = 82)	53.2 (12.5)	45 (54.9)	80 (97.6)	27.7 (4.7)	82 (100)	3 (3.7)	32 (39.0)
Ezetimibe-controlled								
COMBO II (MTD statin)	ALI 75/150 (n = 479)	61.7 (9.4)	360 (75.2)	404 (84.3)	30.0 (5.4)	0	145 (30.3)	461 (96.2)
	EZE (n = 241)	61.3 (9.2)	170 (70.5)	206 (85.5)	30.3 (5.1)	0	76 (31.5)	224 (92.9)
OPTIONS I (atorvastatin 20-40 mg)	ALI 75/150 (n = 104)	63.1 (10.2)	64 (61.5)	91 (87.5)	31.2 (6.9)	12 (11.5)	58 (55.8)	59 (56.7)
	EZE (n = 102)	64.8 (9.6)	67 (65.7)	91 (89.2)	31.2 (5.9)	4 (3.9)	45 (44.1)	66 (64.7)
OPTIONS II (rosuvastatin 10-20 mg)	ALI 75/150 (n = 103)	59.9 (10.2)	59 (57.3)	87 (84.5)	31.0 (6.9)	14 (13.6)	37 (35.9)	60 (58.3)

Study	Group	Age, years, mean (SD)	Male, n (%)	Race, white n (%)	BMI, kg/m^2, mean (SD)	HeFH, n (%)	Type 2 diabetes, n (%)	ASCVD, n (%)
	EZE (n = 101)	61.8 (10.3)	57 (56.4)	88 (87.1)	31.1 (6.4)	14 (13.9)	44 (43.1)	63 (61.8)
ALTERNATIVE (no statin)	ALI 75/150 (n = 126)	64.1 (9.0)	70 (55.6)	117 (92.9)	29.6 (6.6)	14 (11.1)	36 (28.6)	71 (56.3)
	EZE (n = 125)	62.8 (10.1)	67 (53.6)	116 (92.8)	28.4 (4.9)	25 (20.0)	24 (19.2)	58 (46.4)
MONO (no statin)	ALI 75/150 (n = 52)	60.8 (4.6)	28 (53.8)	46 (88.5)	30.1 (5.9)	0	3 (5.8)	0
	EZE (n = 51)	59.6 (5.3)	27 (52.9)	47 (92.2)	28.4 (6.7)	0	1 (2.0)	0

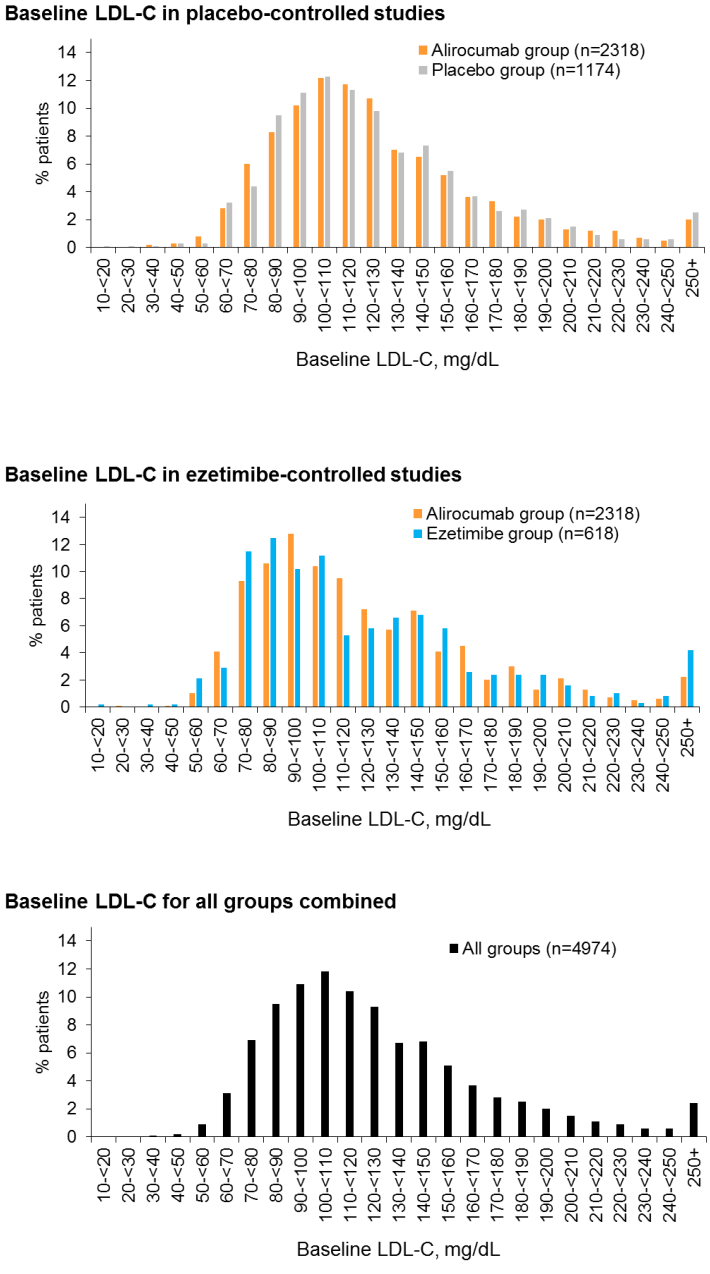
ALI = alirocumab; ASCVD = atherosclerotic cardiovascular disease; atorva = stoarvastatin; BMI = body mass index; EZE = ezetimibe; LDL-C = low-density lipoprotein cholesterol; MTD, maximally tolerated dose of statin; PBO = placebo; Q2W = every 2 weeks: rosuva = rosuvastatin; SD = standard deviation.

eTable 3. Baseline lipid values in individual studies (randomized population)

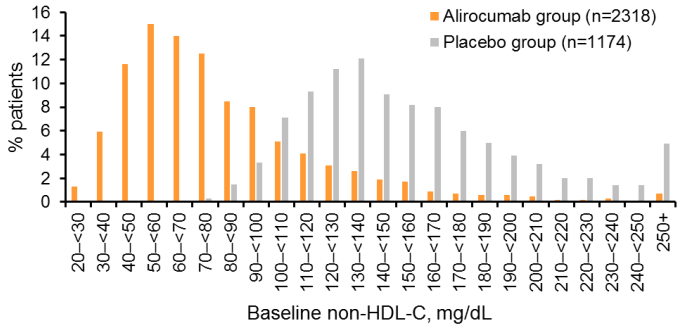
Trial	LONG TERM		HIGH FH		COMBO I		FH I		FH II		COMBO II		OPTIONS I		OPTIONS II		ALTERNATIVE		MONO	
Group	**ALI**	**PBO**	**ALI**	**PBO**	**ALI**	**PBO**	**ALI**	**PBO**	**ALI**	**PBO**	**ALI**	**EZE**	**ALI**	**EZE**	**ALI**	**EZE**	**ALI**	**EZE**	**ALI**	**EZE**
	n=1550	**n=788**	**n=72**	**n=35**	**n=207**	**n=107**	**n=322**	**n=163**	**n=167**	**n=81**	**n=479**	**n=241**	**n=104**	**n=101**	**n=103**	**n=101**	**n=126**	**n=124**	**n=52**	**n=51**
LDL-C	122.7 (42.6)	121.9 (41.4)	196.3 (57.9)	201.0 (43.4)	100.2 (29.5)	106.0 (35.3)	144.8 (51.1)	144.4 (46.8)	134.6 (41.1)	134.0 (41.4)	108.6 (36.5)	104.6 (34.1)	109.6 (36.4)	99.7 (29.2)	113.1 (30.0)	111.1 (45.7)	191.1 (72.7)	193.5 (70.9)	141.1 (27.1)	138.3 (24.5)
non-HDL-C	152.6 (46.6)	152.0 (45.8)	223.9 (58.8)	231.5 (47.6)	130.0 (34.0)	133.4 (39.8)	170.3 (54.6)	169.6 (50.6)	159.0 (44.8)	157.5 (43.7)	139.1 (40.4)	136.8 (40.4)	137.3 (39.3)	126.7 (35.1)	142.1 (37.1)	140.8 (49.8)	230.0 (80.4)	229.8 (82.7)	167.4 (0.3)	164.0 (29.7)
apoB	101.9 (27.7)	101.4 (27.3)	138.2 (32.0)	146.6 (28.3)	90.8 (21.4)	91.4 (24.1)	114.4 (30.8)	113.4 (28.5)	107.9 (27.4)	107.7 (23.9)	94.3 (23.2)	93.5 (23.1)	93.1 (23.7)	86.5 (20.3)	95.8 (21.5)	95.1 (26.4)	141.7 (39.5)	138.2 (37.4)	104.3 (18.4)	104.3 (19.1)

ALI, alirocumab; EZE, ezetimibe; non-HDL-C, non-high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; PBO, placebo. Lipids are means (SD), mg/dL.

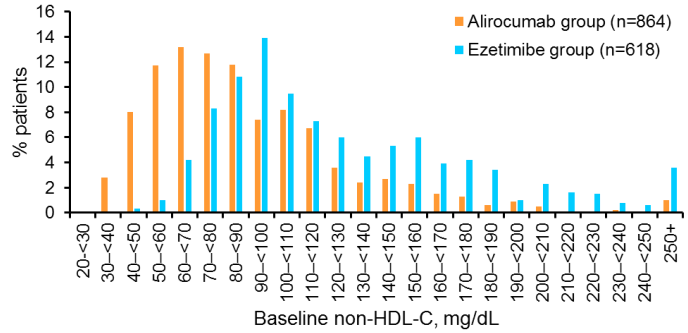
eFigure 2. Distribution of lipid levels at baseline in pooled treatment groups according to control used in the ODYSSEY trials and overall distributions for all groups combined



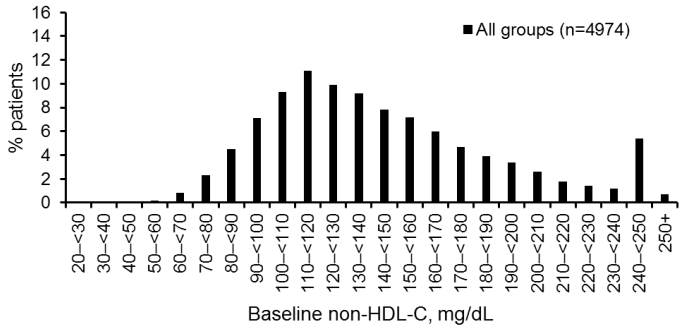
Baseline non-HDL-C in placebo-controlled studies



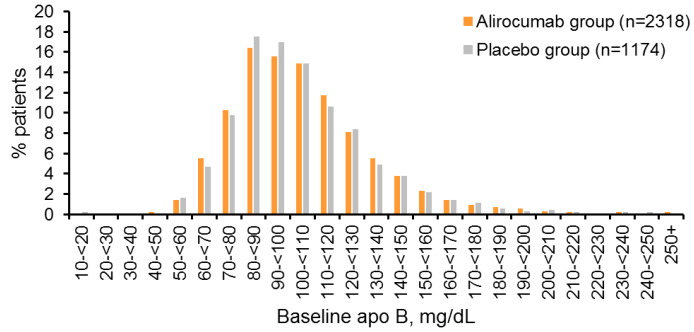
Baseline non-HDL-C in ezetimibe-controlled studies



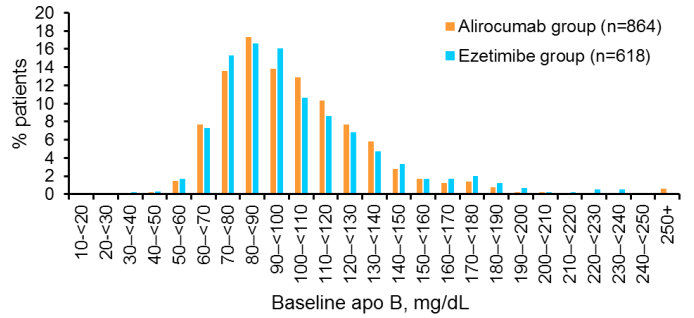
Baseline non-HDL-C for all groups combined



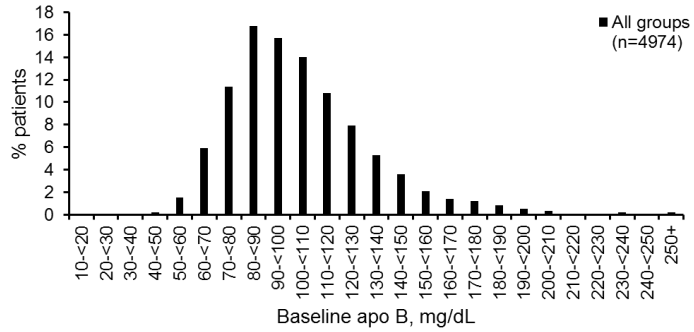
Baseline apo B in placebo-controlled studies



Baseline apo B in ezetimibe-controlled studies



Baseline apo B for all groups combined

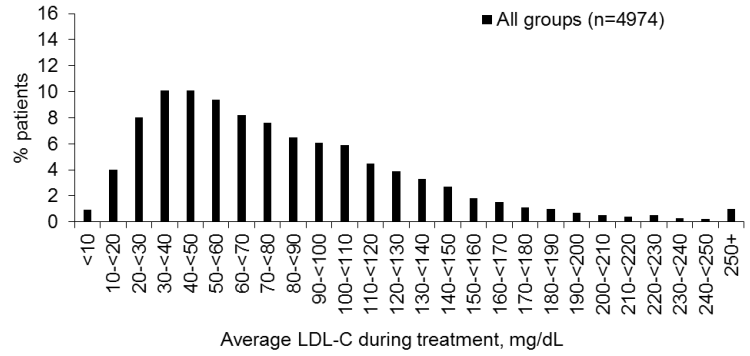


Two patients with missing baseline LDL-C and 3 patients with missing apo B were excluded from the analysis.

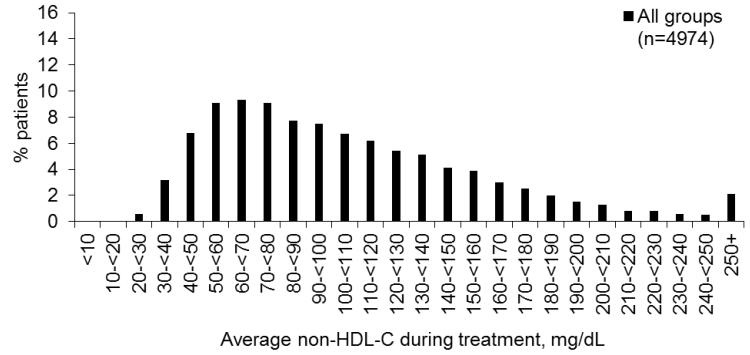
Non-HDL-C, non-high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

eFigure 3. Distribution of average achieved lipid levels and percent reduction in lipids from baseline during treatment for all treatment groups combined

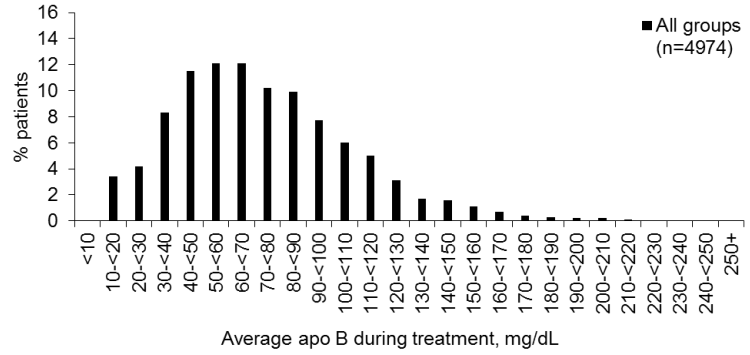
Average LDL-C during treatment - all groups combined



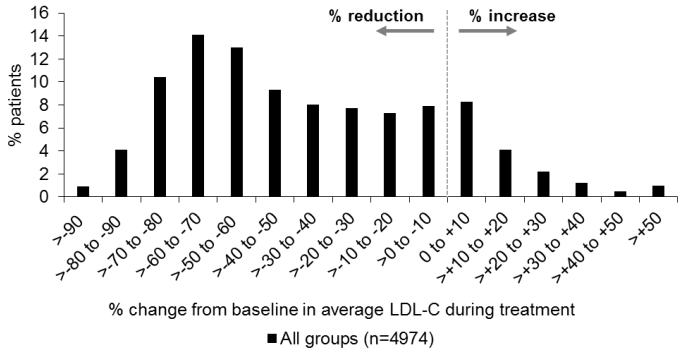
Average non-HDL-C during treatment – all groups combined



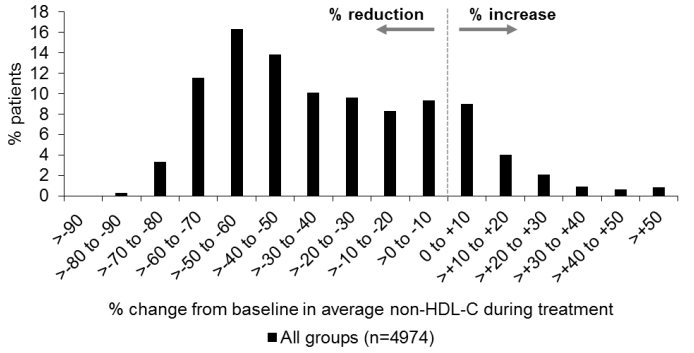
Average apo B during treatment – all groups combined



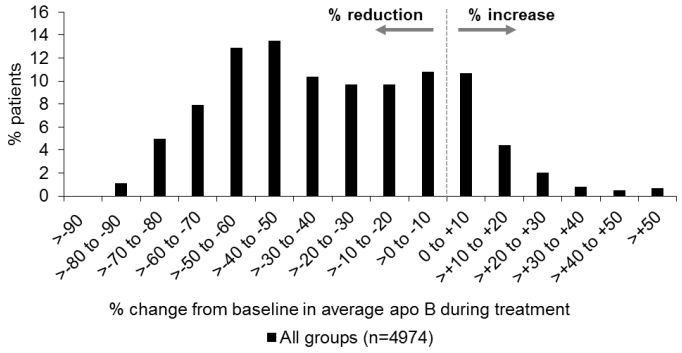
LDL-C average % change from baseline during treatment – all groups combined



Non-HDL-C average % change from baseline during treatment – all groups combined



Apo B average % change from baseline during treatment – all groups combined



Non-HDL-C, non-high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

eTable 4. Average achieved lipid levels and percentage reductions during treatment in individual trials (safety population)

Trial	LONG TERM		HIGH FH		COMBO I		FH I		FH II		COMBO II		OPTIONS I		OPTIONS II		ALTERNATIVE		MONO	
Group	**ALI n=1550**	**PBO n=788**	**ALI n=72**	**PBO n=35**	**ALI n=207**	**PBO n=107**	**ALI n=322**	**PBO n=163**	**ALI n=167**	**PBO n=81**	**ALI n=479**	**EZE n=241**	**ALI n=104**	**EZE n=101**	**ALI n=103**	**EZE n=101**	**ALI n=126**	**EZE n=124**	**ALI n=52**	**EZE n=51**
Average achieved, mg/dL																				
LDL-C	49.8 (34.6)	120.5 (39.0)	111.5 (65.0)	183.9 (47.0)	52.2 (25.6)	102.2 (34.9)	76.3 (41.0)	153.4 (49.1)	68.2 (35.9)	138.7 (41.5)	53.5 (31.4)	82.4 (33.3)	58.7 (33.4)	78.1 (32.2)	67.9 (33.1)	89.3 (42.4)	103.3 (68.0)	160.7 (58.3)	68.3 (20.5)	111.7 (22.6)
non-HDL-C	75.1 (38.1)	151.1 (42.7)	137.5 (65.1)	213.8 (50.2)	80.1 (31.2)	130.4 (38.6)	99.7 (44.3)	181.0 (52.4)	91.0 (39.2)	163.2 (46.3)	80.6 (34.2)	110.2 (38.2)	83.4 (36.8)	103.3 (36.5)	93.1 (38.2)	116.5 (44.3)	135.5 (70.4)	191.6 (64.2)	91.1 (20.3)	135.8 (26.6)
apoB*	51.5 (28.4)	101.0 (26.3)	90.5 (36.2)	136.4 (30.1)	59.5 (20.3)	91.2 (25.8)	71.4 (27.0)	118.9 (29.6)	64.4 (23.7)	107.6 (23.4)	59.0 (22.5)	79.6 (24.2)	58.3 (25.9)	76.3 (25.7)	67.0 (27.3)	83.8 (26.5)	90.2 (38.0)	121.5 (32.2)	65.9 (14.6)	92.8 (17.2)
Average % change from baseline																				

LDL-C†	-59.9	2.3	-42.9	-7.2	46.8	-1.6	-45.8	8.6	-48.6	5.0	-50.1	-19.4	-45.8	-21.4	-40.2	-13.5	-47.5	-15.7	-51.1	-18.7
	(22.1)	(27.6)	(27.4)	(21.5)	(23.7)	(17.5)	(23.8)	(23.8)	(22.2)	(16.5)	(24.6)	(26.3)	(27.1)	(20.3)	(24.7)	(51.7)	(19.0)	(16.0)	(13.0)	(11.0)
non-HDL-C	-50.5	2.0	-38.0	-6.3	-37.7	-0.5	-39.9	8.5	-42.1	4.6	-41.0	-18.0	-38.3	-18.2	-34.4	-13.8	-41.9	-15.7	-44.9	-16.7
	(19.4)	(22.1)	(24.4)	(20.0)	(20.3)	(15.8)	(21.4)	(20.7)	(20.1)	(16.0)	(20.8)	(22.2)	(23.5)	(18.0)	(21.4)	(28.9)	(14.5)	(11.8)	(11.3)	(11.2)
apoB‡	-50.1	2.0	-33.6	-5.6	-34.2	1.5	-36.3	6.2	-39.6	0.8	-36.9	-13.9	-36.4	-12.2	-29.4	-9.2	36.9	-11.1	-36.7	-10.2
	(22.6)	(26.4)	(24.4)	(18.5)	(20.3)	(18.8)	(19.9)	(19.2)	(18.2)	(12.3)	(20.6)	(19.8)	(24.7)	(20.5)	(25.1)	(28.9)	(15.9)	(12.3)	(13.4)	(11.8)

ALI, alirocumab; EZE, ezetimibe; non-HDL-C, non-high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; PBO, placebo. Lipids are means (SD), mg/dL.

For patients with no post-baseline lipid values, baseline values were used. *Two patients with missing baseline and no post-baseline apoB were excluded from the analysis. †Two patients with missing baseline LDL-C were excluded from the analysis. ‡103 patients with missing baseline apoB were excluded from the analysis.

eTable 5. Week 4* achieved lipid levels and percentage reductions in individual trials (safety population)

Trial	LONG TERM		HIGH FH		COMBO I		FH I		FH II		COMBO II		OPTIONS I		OPTIONS II		ALTERN.		MONO		MACE vs average achieved level (pool of all patients from the trials)			
Group	ALI n=1550	PBO n=788	ALI n=72	PBO n=35	ALI n=207	PBO n=107	ALI n=322	PBO n=163	ALI n=167	PBO n=81	ALI n=479	EZE n=241	ALI n=104	EZE n=101	ALI n=103	EZE n=101	ALI n=126	EZE n=124	ALI n=52	EZE n=51				
Average achieved mg/dL																					Category	N	HR (95% CI)	*P*-value
LDL-C	47.9 (37.1)	120.1 (42.5)	100.4 (74.3)	181.7 (51.5)	52.2 (33.0)	101.6 (36.0)	77.8 (43.3)	146.5 (53.8)	76.2 (37.8)	134.3 (43.9)	52.4 (34.4)	76.6 (31.3)	50.4 (30.6)	72.7 (30.6)	62.5 (33.9)	79.0 (36.4)	107.1 (69.8)	156.4 (55.9)	68.0 (20.6)	112.1 (24.7)	Per 39 mg/dL difference	4972	0.79 (0.67 to 0.94)	0.0092
non-HDL-C	71.0 (39.6)	149.5 (46.5)	124.6 (73.0)	209.9 (57.6)	78.3 (37.6)	128.0 (41.3)	100.6 (47.8)	173.5 (57.5)	97.4 (43.6)	156.8 (46.8)	78.2 (38.2)	103.8 (35.7)	73.7 (32.9)	96.8 (36.8)	86.8 (39.7)	104.6 (38.9)	138.8 (79.2)	189.7 (67.0)	91.6 (23.1)	136.5 (29.2)	Per 42 mg/dL decrease	4974	0.81 (0.68 to 0.96)	0.0141
apoB†	48.8 (30.9)	99.5 (27.6)	84.4 (36.2)	131.7 (29.3)	61.4 (25.5)	93.2 (31.7)	75.8 (30.0)	115.6 (29.5)	73.6 (30.2)	105.7 (24.9)	58.6 (24.8)	76.8 (22.8)	60.4 (26.7)	73.3 (23.2)	66.7 (27.9)	81.1 (25.5)	91.2 (37.9)	121.4 (33.1)	66.3 (18.4)	92.1 (17.8)	Per 27 mg/dL decrease	4871	0.79 (0.67 to 0.94)	0.0072
Average % change from baseline																					MACE vs % change in average level			
LDL-C‡	-61.6 (24.3)	1.3 (30.1)	-50.7 (27.2)	-9.4 (19.3)	-48.7 (25.3)	-1.7 (25.0)	-46.1 (22.9)	3.5 (33.3)	-43.7 (20.2)	1.2 (16.0)	-52.0 (26.3)	-24.9 (23.7)	-53.4 (25.4)	-26.4 (22.6)	-45.4 (23.8)	-23.7 (46.4)	-45.9 (18.2)	-18.3 (11.8)	-51.5 (12.8)	-18.6 (12.2)	Per 50% reduction	4972	0.74 (0.60 to 0.90)	0.0030
non-HDL-C	-53.4 (20.1)	0.5 (24.0)	45.1 (23.9)	-9.0 (19.0)	-40.3 (21.0)	-2.4 (20.8)	-40.4 (20.9)	4.0 (29.5)	39.2 (18.8)	0.3 (15.2)	-43.4 (22.5)	-22.3 (21.4)	-45.3 (21.7)	-23.1 (19.4)	-39.5 (20.5)	-22.9 (24.4)	-41.2 (15.0)	-16.9 (11.0)	-45.1 (10.5)	-16.3 (12.1)	Per 50% reduction	4974	0.71 (0.54 to 0.94)	0.0147

apoB[§]	-52.8 (2.54)	0.4 (30.5)	-38.1 (24.4)	-9.1 (16.6)	-32.9 (22.9)	3.2 (21.1)	-32.8 (20.4)	2.9 (18.3)	-31.9 (20.1)	-1.0 (15.1)	-37.7 (21.8)	-16.5 (19.9)	-34.4 (23.8)	-15.0 (16.8)	-29.4 (25.9)	-12.1 (26.4)	-35.3 (19.2)	-11.2 (13.5)	-35.8 (16.7)	-11.1 (13.9)	Per 50% reduction	4871	0.75 (0.61 to 0.92)	0.0064

ALI, alirocumab; ALTERN., ALTERNATIVE; EZE, ezetimibe; non-HDL-C, non-high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; PBO, placebo. Lipids are means (SD), mg/dL. *Week 12 data shown for apoB as no Week 4 values were collected.

For patients with no lipid values at Week 4 (or Week 12 for apoB), baseline values were used. [†]14 patients with missing baseline apoB and no Week 12 apoB were excluded from the analysis. [‡]Two patients with missing baseline LDL-C were excluded from the analysis. [§]103 patients with missing baseline apoB were excluded from the analysis.

eTable 6. Correlation between average LDL-C, non-HDL-C and apoB during the treatment period

	Average LDL-C	**Average non-HDL-C**	**Average apoB**
Average LDL-C during the treatment period	-	0.973 (*P*<0.0001)	0.922 (*P*<0.0001)
Average non-HDL-C during the treatment period	0.973 (*P*<0.0001)	-	0.948 (*P*<0.0001)
Average apoB during the treatment period	0.922 (*P*<0.0001)	0.948 (*P*<0.0001)	-

Pearson correlation coefficient

Non-HDL-C, non-high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

eTable 7. Safety summary for the 10 Phase 3 trials used in this analysis*

	Placebo-controlled trials		Ezetimibe-controlled trials	
n (%)	Alirocumab (n=2318)	Placebo (n=1174)	Alirocumab (n=864)	Ezetimibe (n=618)
TEAEs	1851 (79.9)	954 (81.3)	657 (76.0)	457 (73.9)
Treatment-emergent SAEs	385 (16.6)	202 (17.2)	147 (17.0)	86 (13.9)
TEAEs leading to death	16 (0.7)	13 (1.1)	6 (0.7)	9 (1.5)
TEAEs leading to discontinuation	144 (6.2)	67 (5.7)	84 (9.7)	66 (10.7)
TEAEs in ≥5% of patients				
Nasopharyngitis	291 (12.6)	142 (12.1)	52 (6.0)	41 (6.6)
Injection site reaction	167 (7.2)	62 (5.3)	25 (2.9)	13 (2.1)
Upper respiratory tract infection	162 (7.0)	94 (8.0)	62 (7.2)	40 (6.5)
Influenza	147 (6.3)	63 (5.4)	37 (4.3)	23 (3.7)
Urinary tract infection	128 (5.5)	65 (5.5)	21 (2.4)	25 (4.0)
Back pain	123 (5.3)	70 (6.0)	33 (3.8)	26 (4.2)
Diarrhoea	123 (5.3)	57 (4.9)	30 (3.5)	21 (3.4)
Headache	119 (5.1)	64 (5.5)	43 (5.0)	24 (3.9)

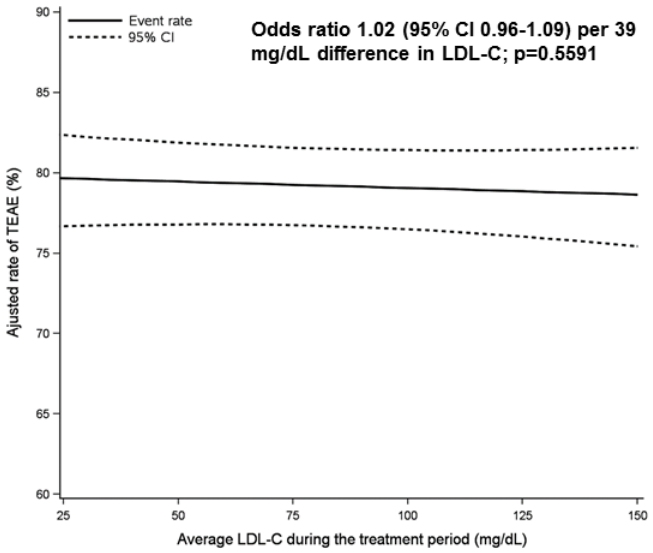
Arthralgia	118 (5.1)	76 (6.5)	42 (4.9)	26 (4.2)
Myalgia	111 (4.8)	46 (3.9)	62 (7.2)	48 (7.8)
Accidental overdose	30 (1.3)	17 (1.4)	54 (6.3)	24 (3.9)

SAE, serious adverse event; TEAE, treatment-emergent adverse event.

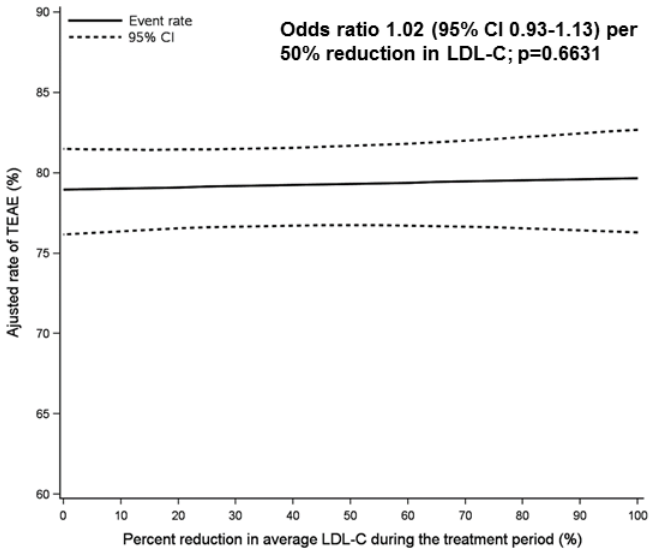
*Placebo-controlled studies: Phase 3 (LONG TERM, FH I, FH II, HIGH FH, COMBO I); ezetimibe-controlled studies: Phase 3 (COMBO II, OPTIONS I, OPTIONS II, ALTERNATIVE, MONO).

eFigure 4. Adjusted rate of any TEAE by average LDL-C during treatment period: (A) achieved LDL-C during treatment, (B) percentage reduction in LDL-C from baseline (multivariate analysis adjusted on baseline characteristics; pool of Phase 3 studies)

A



B



LDL-C, low-density lipoprotein cholesterol; TEAE, treatment-emergent adverse event.